SYNTHESIS OF [F-18]-ZD1839 AS A PET IMAGING AGENT FOR EPIDERMAL GROWTH FACTOR RECEPTORS

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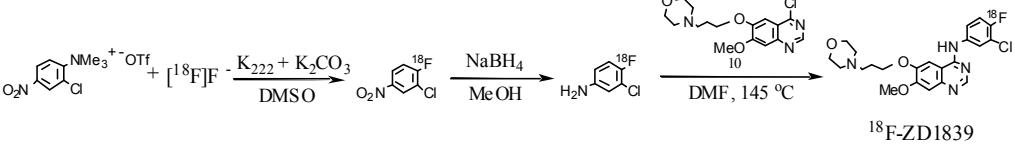
Keywords: ZD1839, Iressa, EGFR, cell signaling, cancer

The epidermal growth factor receptor (EGFR) is an epithelial cell membrane receptor with an intra- cellular tyrosine kinase (TK) component. EGFR-TK is involved in cell signalling critical to proliferation, apoptosis, repair and angiogenesis. More than two thirds of human cancers derive from epithelial tissues and the EFGR-TK is overexpressed in the majority of these tumors. Thus in recent years numerous selective EGFR-TK inhibitors with nanomolar affinities have been developed as potential anti-cancer agents. One potent inhibitor that has progressed the furthest toward clinical registration is ZD1839 (or Iressa). ZD1839 is approved for clinical use in Japan and is close to obtaining U.S. FDA approval. ZD1839 is a fluorine-containing anilinoquinazoline which can be isotopically labelled with ^{18}F for use in clinical oncology as a PET imaging agent. Since extensive pre-clinical and clinical data on ZD1839 are available, the use of ^{18}F-ZD1839 to identify patients who would benefit from Iressa treatment and monitor its efficacy would be straightforward.

While there have been studies on several EGFR-targeted PET imaging agents (1-6), results reported so far with these tracers have been disappointing. We recently began the development of a reliable and efficient synthetic route for the routine preparation of ^{18}F-ZD1839. Starting from 2-nitro-4,5-dimethoxybenzoic acid methyl ester, a 9-step synthesis was performed to prepare 7-methoxy-6-(3-morpholinopropoxy)-4-chloro-quinazoline (compound 10 below). This product was authenticated by proton NMR. Adapting methods reported by others (3-5), ^{18}F-ZD1839 was prepared starting with the standard Kryptofix-K_2CO_3-mediated nucleophilic ^{18}F exchange reaction with a trimethylammonium triflate precursor to give 4-[^{18}F]fluoro-3-chloro-nitrobenzene (Scheme 1) with 50% non-decay corrected yield. Reduction with sodium borohydride gave 4-[^{18}F]fluoro-3-chloro-aniline then condensation with compound 10 in DMF at 145 ^{o}C gave ^{18}F-ZD1839. The overall non-decay corrected ^{18}F-ZD1839 yield based on the starting ^{18}F-fluoride was 7%-10% after 150 min total reaction time including semi-preparative reverse phase HPLC purification.

Initial biodistribution studies in normal HSD-ICR mice showed high uptake of ^{18}F-ZD1839 in the GI tract, liver, kidneys and bladder consistent with the known high EGFR localization in these organs. Plasma metabolite analysis in several mice up to 3 hr showed temporally decreasing percentage of unchanged ^{18}F-ZD1839 declining to 52% at 3 hr postinjection. Dynamic PET studies of mice using a Concorde microPET P4 scanner are underway.



Scheme 1

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CARBON-11 LABELING OF -DIMETHYLAMINO-BUT-2-ENOIC ACID [4-(PHENYLAMINO)-QUINAZOLIN-6-YL]-AMIDES, A NEW CLASS OF EGFR IRREVERSIBLE INHIBITORS

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Key words: EGFR, PET, cancer, carbon-11

The Epidermal Growth Factor Receptor (EGFR/Her-1/) is involved in proliferation and differentiation of normal and malignant cells. Overexpression of EGFR is present in several cancers such as non-small cell lung carcinoma, breast cancer, brain glioma and prostate cancer. EGFR is an attractive target for the development of labeled compounds that may serve as a diagnostic tool for the treatment of cancer. We synthesized four new groups of irreversible tyrosine kinase (TK) inhibitors as ligands for labeling with carbon-11 or other radioisotopes. A carbon-11 radiosynthesis route was developed for one of theses groups, the -dimethylamino-but-2-enoic acid [4-(phenylamino)-quinazolin-6-yl]-amides group (group C). The [C-11]MeI module of Nuclear Interface was used to label group C at the mono-methyl amine moiety. The labeled inhibitors were obtained after 40 minutes radiosynthesis time with 14% radiochemical yield (EOB), 100% radiochemical purity, 98% chemical purity and specific activity of 3.2 Ci/µmol EOB. The ability of group C to inhibit the autophosphorylation of EGFR-TK was screened by ELISA. The curve of one of the compounds, ML04 for example, gave an IC_{50} of 0.061+/-0.011 nM indicating a high potency of ML04 towards EGFR-TK. In-vitro experiments in intact A431 cells showed that eight hours post incubation with 10nM of ML04 85% inhibition effect was obtained, reflecting the irreversible binding nature of ML04. In an A431 cell study with [C-11]ML04, 78% specific binding was obtained, an increase of 10% relative to [C-11]ML03 (Ortu et al., 2002). At this stage, preliminary in-vivo biodistribution studies of [C-11]ML04 in tumor-bearing (A431) rats were initiated. A maximum %ID/gr tumor/blood ratio of 2.5 was obtained during the first hour post [C-11]ML04 administration. This is a significant improvement over the tumor/blood ratios of [C-11]ML03 and [F-18]ML01, which did not exceed unity over the same time frame (Ortu et al., 2002, Bonasera et al., 2001). [C-11]ML04 tumor uptake of 0.12%Injected-Dose/gr (ID/gr) (ML03, 0.09%ID/gr) and 0.16%ID/gr (ML03, 0.05%ID/gr) were measured at 30 and 60 minutes post injection, a threefold increase relative to ML03. Tumor uptake of [C-11]ML04 increased while tumor uptake of [C-11]ML03 decreased with time. During initial in-vivo metabolic studies of [C-11]ML04, 40% of [C-11]ML04 remained intact in blood 30 minutes post injection, whereas the value for [C-11]ML03 was 17%.

In summary, the positive results on the radio-synthesis and biological analysis of novel compounds such as -Dimethylamino-but-2-enoic acid [4-(phenylamino)-quinazolin-6-yl]-amides, that can specifically bind and inhibit TK activity in cancer cells represent a positive step toward the development of new diagnostic and therapeutic agents for the treatment of cancer.

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RADIOSYNTHESIS OF [^{11}C]DOCETAXEL

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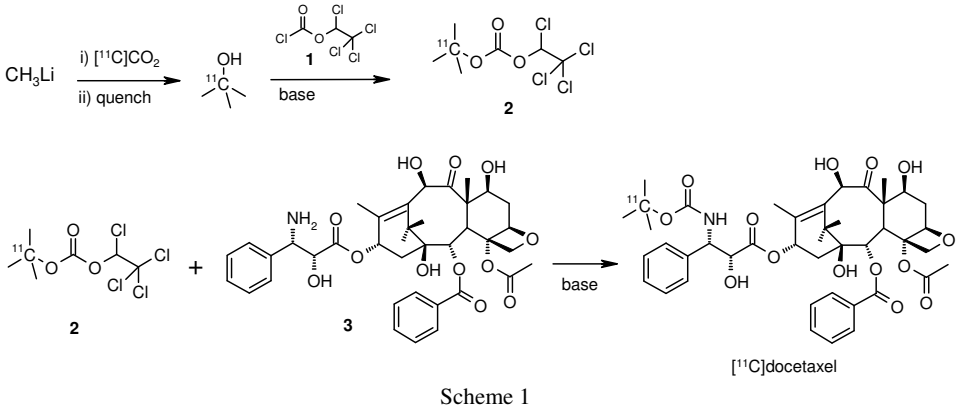
Keywords: [^{11}C]*tert*-Butanol, *tert*-Butoxycarbonylation, [^{11}C]Docetaxel

Docetaxel (taxotere®) is an accepted chemotherapeutic agent for the treatment of patients with breast cancer and non-small cell lung cancers. Reported response rates are in the order of 50 to 60 %. Clearly, methods that are able to predict response to docetaxel treatment would be very useful, as non-responders could be offered alternative therapies at a much earlier stage without suffering side-effects from (ineffective) docetaxel administration. A potential means of predicting response is measuring tumor uptake of docetaxel labeled with a positron emitter such as [^{11}C], using Positron Emission Tomography (PET).

In this study, a radiochemical route was developed for the synthesis of [^{11}C]docetaxel. The radiolabel was successfully introduced in the side-chain by the [^{11}C]*tert*-butoxycarbonylation of the free amine of docetaxel (**3**). [^{11}C]*tert*-Butanol was prepared from [^{11}C]CO_2 and methyl lithium. The mechanism of this reaction has been suggested to be kinetically controlled, and the quantity of [^{11}C]*tert*-butanol can be maximized by increasing the excess of methyl lithium.



Scheme 1

After quantitative formation, [^{11}C]*tert*-butanol was distilled into a second reaction vessel, containing 1,2,2,2-tetrachloroethyl chloroformate (**1**). Heating in the presence of a base yielded [^{11}C]*tert*-butyl-1,2,2,2-tetrachloroethyl carbonate (**2**) in good yield (86±5 %, from [^{11}C]CO_2, decay corrected). The excess of **1** was removed by solid phase extraction and subsequent addition of the amine **3** resulted in [^{11}C]docetaxel.

In conclusion, [^{11}C]docetaxel was obtained in a satisfactory decay corrected yield (15-20%, from [^{11}C]CO_2). After optimizing the purification and formulation, [^{11}C]docetaxel will be produced according to GMP standards for initial PET studies in patients with breast or non-small cell lung cancer.

NON-INVASIVE DETERMINATION OF αvβ3 EXPRESSION USING THE RADIOLABELED RGD-MIMETIC [^{18}F]GBHO-2

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Keywords: non-peptide integrin antagonist, alpha(v)beta3, F-18, oncology

The integrin αvβ3 plays an important role in restenosis, osteoporosis, inflammatory processes as well as metastasis and tumor-induced angiogenesis. Several studies using different murine tumor models showed that radiolabeled RGD-containing peptides allow non-invasive determination of αvβ3 expression. Extensive structure/activity investigations also resulted in peptidomimetics with high αvβ3 affinity and selectivity. Here we introduce the synthesis and biological evaluation of the ^{18}F-labeled RGD-mimetic 5-[N'-(3-**g**uanidino**b**enzoyl)-**h**ydrazino]-3-[N-(4-[^{18}F]fluoro-benzoyl)]-amino-5-**o**xopentanoic acid ([^{18}F]GBHO-2) for the non-invasive determination of αvβ3 expression.

The synthesis of 5-[N'-(3-guanidinobenzoyl)-hydrazino]-3-amino-5-oxopentanoic acid was carried out using solid phase chemistry with Fmoc-strategy. For ^{18}F-labeling N-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) was used. In vitro binding studies were carried out using the isolated immobilized integrins αvβ3, αvβ5, and αIIbβ3. Human melanoma M21 (αvβ3 positive) and melanoma M21-L (αvβ3 negative) bearing nude mice were used for in vivo studies.

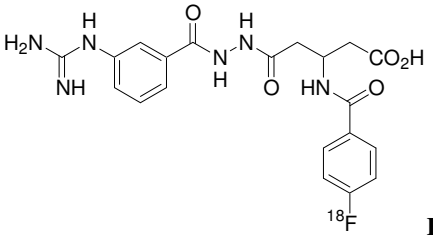

Figure: Structure of [^{18}F]GBHO-2

Labeling of the unprotected RGD-mimetic using [^{18}F]SFB resulted in [^{18}F]GBHO-2 with approx. 65% radiochemical yield. In vitro binding studies revealed high αvβ3 affinity and selectivity for [F-19]GBHO-2 (IC_{50}(αvβ3/Vn) = 8,2 nM; IC_{50}(αvβ5/Vn) and IC_{50}(αIIbβ3/Fb) > 10,000 nM). Biodistribution data showed rapid elimination of the tracer from the blood (0.03 ± 0.01% ID/g 120 min p.i.). Activity concentration in kidneys and liver were very similar at 120 min p.i. (0.2 ± 0.06% ID/g and 0.2 ± 0.05% ID/g, respectively). Activity accumulation in the αvβ3-positive tumor was 2.13 ± 0.10% ID/g 10 min p.i. decreasing to 0.61 ± 0.13% ID/g 120 min p.i.. This results in high tumor/back ground ratios 120 min p.i. (tumor/blood: 18.2, tumor/muscle 35.6, tumor/kidney: 3.3, tumor/liver: 3.0). For the αvβ3-negative tumor approx. 3-times lower activity accumulation was found compared with the receptor expressing tumor. Intravenous injection of 18 mg of the αvβ3 seclective cyclo(-Arg-Gly-Asp-DPhe-Val-) 10 min prior to tracer injection reduced activity accumulation in the melanoma M21 60 min p.i. by approx. 70%.

In conclusion, [^{18}F]GBHO-2 is the first ^{18}F-labeled non-peptidic αvβ3 antagonist showing receptor specific accumulation in αvβ3-positive melanoma M21 and high tumor/background ratios in vivo. In addition, the tracer demonstrated higher αvβ3-selectivity and allows easier labeling compared with [^{18}F]Galacto-RGD. Thus, this ^{18}F-labeled RGD-mimetic is a promising alternative to the non-invasive determination of αvβ3 expression using radiolabeled RGD-peptides.

RADIOLABELED MATRIX METALLOPROTEINASE INHIBITORS WITH HIGH UPTAKE IN MOUSE TUMOR MODELS

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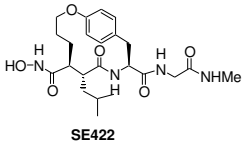
Keywords: matrix metalloproteinase inhibitor, tumor imaging

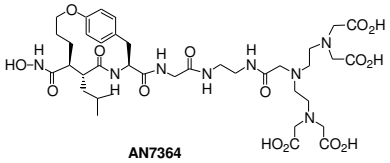
Matrix metalloproteinases (MMPs) are a family of zinc-containing proteases which include collagenases, stromelysins, and gelatinases. They have been implicated in a variety of inflammatory and malignant disease states such as arthritis and cancer, and have been targets for therapeutic intervention for more than a decade[1]. In particular, the Type IV collagenases, MMP-2 and MMP-9, have been shown to be upregulated in tumor vasculature relative to normal tissue, and implicated in both tumor angiogenesis and metastasis[2].

This paper presents our work with MMP inhibitor conjugates to image sites of high MMP concentration. Xue *et al.* reported on a series of pan-MMP inhibitors (such as **SE422**) based upon macrocyclization of succinic acid hydroxamates.[3] We have used these inhibitors as a base for the synthesis of ^{111}In and ^{99m}Tc conjugates which could localize in tumors. The exocyclic amide of these molecules directs into the P_3' pocket, which has been reported as a "solvent exposed" pocket which has minimal impact on selectivity[1]. This tolerance for substitution was the reason this site was initially chosen for derivatization. The macrocycles were conjugated with alkyl, aryl, and PEG linkers to either HYNIC or DTPA and labeled with Tc-99m or In-111, respectively. The uncoordinated conjugates (such as **AN7364**) exhibited comparable activities in *in vitro* assays relative to the parent compounds. An inactive diastereoisomer was also synthesized for use as a negative control.



SE422

	(K_i, nM)
MMP-1	3
MMP-2	1.1
MMP-3	14
MMP-7	0.8
MMP-8	0.5
MMP-9	0.9
MMP-13	0.5
ADAM-17	12



AN7364

	(K_i, nM)
MMP-1	4
MMP-2	7
MMP-3	42
MMP-7	3
MMP-8	0.5
MMP-9	6
MMP-13	3
ADAM-17	34

Biodistributions were carried out in both an Oncomouse model and an HT1080 xenograft model. Significantly higher levels of uptake into the tumor were found in the HT1080 model (18% ID/g for the pictured analog as the In-111 conjugate) than in the Oncomouse (6% ID/g). This result is consistent with the reported elevated expression of MMPs in the HT1080 cell line,[4] which is one of the reasons this model was chosen for the initial screening. Variations in uptake were also seen depending upon the linker/chelate combination. Details of the synthesis, radiolabeling, biodistribution, and imaging of these compounds will be presented.

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INVESTIGATION OF A NEW SIGMA 2 RECEPTOR LIGAND FOR DETECTION OF BREAST CANCER

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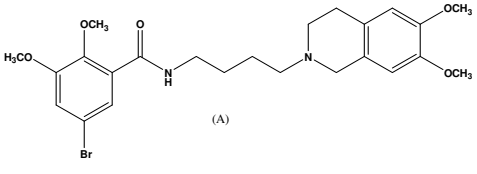
Keywords: Sigma 2, ^{76}Br, Breast Cancer, PET Imaging

Sigma (σ) receptors have been identified as a distinct class of receptors that are expressed in liver, kidneys, endocrine glands and in the central nervous system. Apart from the normal expression of the sigma receptor in these tissues, several studies have reported its overexpression in both human and murine tumors (1-3). It has also been shown that there are two types of this receptor, σ_1 and σ_2. More recent studies have shown the expression of σ_2 to be a reliable biomarker for the proliferative status of solid tumors (4,5). Up regulation of σ_2 receptors during proliferation was shown by selectively recruiting cells into quiescent and proliferative states and then measuring the receptor concentration (4). It was found that σ_2 receptor concentrations increased tenfold when cells were recruited to proliferative states. Therefore, radioligands that have both high affinity and high selectivity for σ_2 receptors should be good tracers for the non-invasive assessment of the proliferative status of human solid tumors using PET or SPECT. To this end, a high affinity and highly selective σ_2 radioligand has been developed for the assessment of tumor status.



(A)

The σ_2 radioligand (A), was labeled with ^{76}Br via an electrophillic destannylation reaction. The reaction takes place under aqueous (200 µL Milli-Q) conditions in the presence of 5% peracetic acid/acetic acid (40 µL) for 40 min. (A) was purified via HPLC with yields typically between 50 – 60%.

This compound was studied in mature Balb/C mice that were implanted with EMT-6 mammary tumors. The mice were implanted in the nape of the neck 7 days prior to the study. The biodistribution study consisted of three groups: 1 hr low dose (~6 µCi), 4hr low dose and a 4 hr high dose (~150 µCi). The %ID/g at 1 hr for tumor, brain, fat, blood and liver were 4.0±0.4, 0.25±0.02, 1.1±0.4, 2.1±0.3 and 5.4±0.4, respectively. At 4 hr for the low dose animals the values decreased to 1.2±0.2, 0.15±0.02, 0.3±0.2, 0.82±0.08 and 1.3±0.2, respectively. The %ID/g for the 4 hr high dose animals was not significantly different. The activity injected into the high dose animals was enough to perform microPET imaging studies. At 1 and 2 hr the tumors were clearly identified in the three animals that were injected. This initial study has shown that this σ_2 receptor compound has a high uptake into EMT-6 mammary tumors and can be imaged non-invasively.

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MICROPET IMAGING AND BIODISTRIBUTION STUDIES OF THE SIGMA-1 RECEPTOR RADIOTRACER [^{18}F]FPS IN THE MMTV TRANSGENIC MOUSE BREAST CANCER MODEL.

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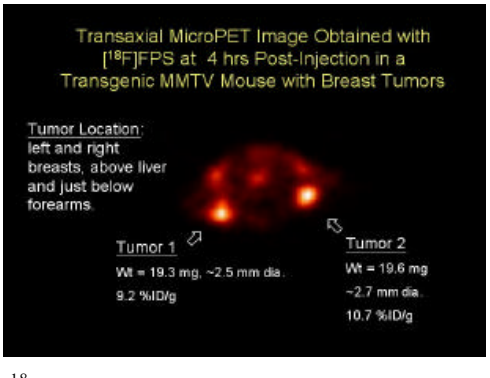
Introduction: Increased expression of sigma-1 receptors have been reported in several human malignancies, including breast cancer where sigma-1 receptor densities have been correlated positively with Bcl_2 expression and inversely with progesterone receptor expression [1]. To identify an effective sigma-1 receptor targeted tumor imaging agent, we evaluated the novel PET radioligand [^{18}F]1-(3-flouropropyl)-4-[4-(cyanophenoxy)methyl]piperidine, [^{18}F]FPS (KD = 0.5 nM) in MMTV transgenic mice with palpable breast tumors.

Methods: High specific activity [^{18}F]FPS (1.92 ± 0.41 Ci/µmol EOS; dose: 1 mCi for MicroPET; 15 µCi for biodistribution studies) was administered iv over 5 seconds to adult MMTV mice with palpable breast tumors. Biodistribution data at 1 hr and 4 hr post-injection were correlated with microPET imaging data (Concorde R4, Knoxville TN). Specific binding at 4 hr was determined by pretreatment with FPS or the sigma receptor binding drug haloperidol (1 mg/kg, iv).



Results**:** Biodistribution analysis demonstrated that [^{18}F]FPS tumor uptake and tumor/tissue ratios were greater at 4 hr than at 1 hr. At 4 hr, tumor uptake was 10.7 ± 2.1 %ID/g, and tumor/tissue ratios for the blood, lung, muscle, heart, kidney and liver were 48.9, 1.7, 9.0, 4.9, 2.3 and 0.3 respectively (n = 9). MicroPET imaging in 3 mice allowed for clear visualization of all palpable tumors by 4 hr (Figure 1; 22/22 lesions, 19-200 mg in size), with SUVs ranging from 1.8 to 3.4. Tumor uptake was reduced significantly by the preadministration of FPS or haloperidol [Table I: Tumor %ID/g (4 hr) = saline control: 10.7 ± 2.1, n = 9; FPS: 0.89 ± 0.28, -92%, $p < 0.001$, n = 4; haloperidol: 2.09 ± 0.64, -79%, $p < 0.001$, n = 3]. [^{18}F]FPS binding to sigma receptors in the liver, brain, muscle, heart, kidney, lung and spleen was also significantly blocked (71-91%).

Table I.

Condition	Blood	Brain	Heart	Lung	Muscle	Tumor (solid)
Control 4 hr	0.23 ± 0.07	7.57 ± 1.79	2.24 ± 0.63	6.13 ± 1.01	1.20 ± 0.35	10.70 ± 2.09
Haldol	0.60 ± 0.08	1.49 ± 0.35	1.01 ± 0.15	1.87 ± 0.67	1.00 ± 0.11	2.09 ± 0.64
diff	157	-80	-55	-69	-17	-79
p	0.0001	0.0005	0.0119	0.0002	0.3693	0.0002
FPS	0.49 ± 0.11	0.68 ± 0.08	0.46 ± 0.22	1.01 ± 0.24	0.35 ± 0.03	0.89 ± 0.28
diff	108	-91	-79	-83	-71	-92
p	0.0009	0.0000	0.0005	0.0000	0.0010	0.0000

Conclusion: In the MMTV mouse model, [^{18}F]FPS exhibited high and saturable tumor uptake and excellent tumor/tissue ratios by 4 hrs for most organs. Further studies are warranted to assess the effectiveness of [^{18}F]FPS for the visualization of malignant breast lesions in humans.

Reference: [1] Simony-Lafontaine *et al. Br J Cancer*, 2000 Jun;82(12):1958-66.

SYNTHESIS OF RHENIUM/TECHNETIUM LABELED ESTROGEN RECEPTOR IMAGING AGENTS: EVALUATION USING MICROPET WITH TECHNETIUM-94M

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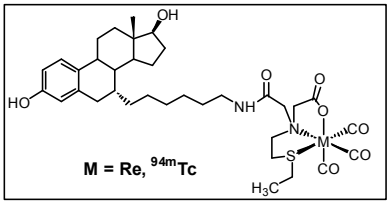
Keywords: Rhenium, Technetium, Tricarbonyl, Technetium-94m, MicroPET

We are interested in the development of rhenium and technetium-labeled estradiol derivatives for use as imaging agents of estrogen receptor (ER)-positive breast tumors. We have, therefore, prepared tridentate metal tricarbonyl chelates, substituted at the 7 and 17 positions of estradiol. To explore estradiol derivatives containing rhenium or technetium tricarbonyl with a tridentate chelation core, two novel chelating systems were prepared. The first chelate utilizes iminodiacetic acid and a thioether, the second employs a carboxylic acid and two thioethers. As there is no non-radioactive isotope, rhenium was used as a congener for technetium in the characterization and ER binding affinity studies of the conjugates. The positron emitting Tc-94m, rather than the more commonly used Tc-99m isotope, was selected for the *in vivo* evaluation studies, as this isotope may be imaged using positron emission tomography, with which rapid and quantitative biodistribution data may be obtained from imaging small numbers of animals.

It was demonstrated that some of the $Re(CO)_3$ conjugates synthesized, especially those with the metal tricarbonyl moiety tethered at the 7 position of estradiol, had high binding for the ER *in vitro*. The rhenium conjugate with the highest overall ER affinity, shown below, had relative binding affinities of 18 1, 27 3, 38 2% for cytosol, ER , and ER , respectively (relative to 100% for the estradiol standard). This conjugate was labeled with Tc-94m by a sodium borohydride reduction of $^{94m}TcO_4^-$, produced as previously reported (1, 2), in the presence of CO(g) to give the triaqua cation $^{94m}Tc(CO)_3^+$, then adding the free chelate and heating at 80° C for 20 minutes, followed by HPLC purification.



To determine whether using a neutral, tridentate metal tricarbonyl chelation unit would result in improved uptake in ER-rich tissues of an animal model, *in vivo* biodistribution and microPET imaging studies were carried out in female Sprague Dawley rats. The tissue dissection studies did not show target tissue-selective uptake, nor was the uptake in ER-rich organs blocked by the co-administration of estradiol. While the microPET imaging study concurred with the results of the biodistribution study, this study did identify the stomach as a major site of activity deposition, a site that might have been missed by standard tissue distribution studies. Synthesis, binding affinities, *in vivo* biodistribution, and microPET imaging data will be presented.

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EX VIVO PHARMACOLOGICAL EVALUATION OF THE PERIPHERAL BENZODIAZEPINE RECEPTOR RADIOLIGAND [^{123}I]-CLINDE IN ANIMAL TUMOUR MODELS

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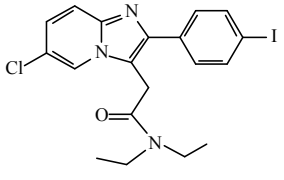
Keywords: Imidazopyridines, PBR, Melanoma, Breast tumours, SPECT

The peripheral benzodiazepine receptors (PBRs) are over-expressed in neoplastic tissue, neurodegenerative diseases and inflammation. In particular, enhanced PBR density was observed in breast, melanoma, glial and prostate tumours. A number of halogenated imidazopyridines have been prepared by our group with high affinity and selectivity for the PBRs, several of which can be radiolabelled with either iodine-123 or 125 as well as fluorine-18 and carbon-11. The aim of this study was to evaluate the iodine-123 labelled imidazopyridine: N,N-diethyl-6-chloro-(4'-iodophenyl)imidazo(1,2-a)pyridine-3-acetamide ([^{123}I]-CLINDE) **1,** as a potent radioligand for the PBRs (IC_{50} = 1.7 nM) in tumour bearing rodents.



1

Radiolabelling was achieved by classical [^{123}I]iododestannylation of the tributyltin precursor using peracetic acid. Purification by C-18 reverse phase HPLC gave [^{123}I]-CLINDE in 70-85% radiochemical yield and in greater than 98% radiochemical purity.

Human melanoma A375 cells were injected subcutaneously in the left shoulder of 6 weeks old Balb/c nude mice. *In vivo* biodistribution studies were undertaken 24 days after injection of the cells with tumour masses in the range of 150-250 mg. Rat mammary adenocarcinoma cells (13762 MAT) were injected subcutaneously in the left shoulder of 14 week old Fisher 344 rats. *In vivo* studies were performed 12 days after injection of the cells with tumour masses in the range of 1.5-2.0 g. Basic images were performed on GE Starcam -camera.

Biodistribution studies in mice implanted with the A375 melanoma cells indicated high tumour uptake (2.5-3.0 % ID/g) of [^{123}I]-CLINDE, which was retained to at least 48 h resulting in a tumour to blood (T/B) ratio greater than 7. In the Fischer rats implanted with the adenocarcinoma a similar pattern of uptake was observed with a peak uptake of 0.9-1 % ID/g also retained over 48 h. Pre-administration of PK 11195 (5 mg/kg, i.v.) markedly reduced the uptake of activity in both tumours and in tissues expressing the PBR thus confirming the specificity of the tracers for the PBR. *In vivo* -imaging of [^{123}I]-CLINDE in fisher rats implanted with mammary adenocarcinomas indicated significant contrast in the tumours compared to normal tissue. The uptake in the tumour increase with time whilst undergoing clearance from other tissue. Metabolite studies indicated that the activity extracted from both tumours as well as from organs expressing the PBR was the intact tracer.

These results indicate that the imidazopyridine [^{123}I]-CLINDE labelled with either iodine-123 or other PET isotopes are promising ligands for the study of the PBR in a variety of tumours.